104. (NEW) The method of claim 103, wherein the overexpressed recombinant intimin comprises a histidine-tag, and wherein the histidine-tag is optionally removed prior to administration.

REMARKS

I. Status of the Claims

In the previous Amendment, claim 72 was cancelled, claims 60, 66-70, 73-82, and 84-85 were amended, and claims 91-96 were added. Thus, claims 60, 66-71, and 73-96 are currently pending. The present Amendment under 37 C.F.R. § 1.116 proposes the addition of claims 97-104, depending from independent claims 60, 73, 76, and 96. New claims 97, 99, 101, and 103 recite that the "enriched or purified intimin" described, for example, in claims 60, 73, 76, and 96 is "overexpressed recombinant intimin," while new claims 98, 100, 102, and 104 recite that the "overexpressed recombinant intimin" also "comprises a histidine-tag" which is "optionally removed prior to administration." Applicants submit that the proposed new claims do not raise new issues or require any additional search of the art. Therefore, this Amendment should allow for immediate action, and Applicants respectfully request the entry of the new claims, leaving claims 60, 66-71, and 73-104 pending in this application.

Support for the new claims may be found in the application as a whole. For example, page 19, line 15, provides explicit written support for "overexpressed recombinant intimin," while the term "histidine-tag" is expressly recited at many locations throughout the specification. Examples 1-3 at pages 21-38 describe a method of

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

preparing enriched or purified overexpressed recombinant intimin by using a vector that includes a DNA sequence encoding a six-histidine tag. In addition, the text from page 14, line 7, to page 16, line 11, comments that the intimin administered to a host may be histidine-tagged, or may be prepared from histidine-tagged intimin from which the tag has been removed.

II. Rejections Withdrawn

Applicants acknowledge with appreciation the withdrawal of the rejections of claims 66, 68-75, 77-79, and 82 under 35 U.S.C. § 112, first and second paragraphs, claims 60, 66, 71, 76, and 87 under § 102(b), and of claims 60, 66-70, 76-77, 83, 85-86, and 89-90 under § 103(a) over Dougan et al. ("Dougan"; U.S. Patent 5,747,293). (Office Action at pages 2-3, paragraphs 2-7.) Applicants thank the Examiner for her time and for the courtesies extended to Applicants' representatives in the interview of December, 2001, during which these rejections were discussed.

III. Rejections Maintained

A. Rejection of claims 60, 66-71, 73-88, and 91-94: Chidlow in view of Craviato

The Office rejected these claims under 35 U.S.C. § 103(a) over Chidlow in view of Craviato et al. ("Craviato"; *J. Infect. Dis.*, 163: 1247-55 (1991)). (Office Action at page 3, paragraph 8.) Applicants respectfully traverse.

As described in the Office Action of August 15, 2001, the Office relied on Chidlow for a teaching of "generating antibodies in a host" and "administering the antibodies in an effective amount to provide passive immune protection in the patient." (Office Action of August 15, 2001, at page 14.) The Office noted, however, that Chidlow does not

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

teach anti-intimin antibodies, "purified" intimin, or anti-intimin antibodies that are able to block binding to mammalian cells. (Office Action of August 15, 2001, at page 15.) The Office relied on Craviato for a teaching of "purified intimin," but also acknowledged that Craviato does not teach "administering" anti-intimin antibodies. (*Id.*; Office Action of October 4, 2002, at page 3.) The present Office Action extends this rejection to the amended and new claims. (Office Action of October 4, 2002, at pages 4-5.)

Applicants respectfully submit that the combination of Chidlow and Craviato does not render any of the instant claims obvious. Not only does Chidlow not teach anti-intimin antibodies or "purified" intimin but, in fact, Chidlow's teachings do not relate to intimin at all. Instead, Chidlow discusses endotoxins and exotoxins. Intimin is not an endotoxin or exotoxin, but an adherence factor. (Specification at page 3, lines 17-20.) Thus, there is nothing in Chidlow to provide one of ordinary skill in the art with a motivation to administer intimin to a host.

Craviato does not remedy the deficiency of Chidlow. Craviato's disclosure relates to disease-producing bacteria in which intimin is in the natural concentration produced during infectious disease. It does not suggest that it would be desirable to administer "enriched or purified intimin" to a host. As explained in the remarks filed January 29, 2002, the "enriched or purified intimin" does not include the intimin released from bacteria naturally present in a host in the course of a disease-producing infection in that same host. The intimin described in Craviato is present in its natural concentration in the infectious bacteria, and so, is not "enriched."

One of ordinary skill in the art applying the teachings of Chidlow in view of Craviato would recognize the suggestions in Chidlow that beneficial immune responses

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

may be obtained by administering endotoxins, exotoxins, and other cellular materials together, not by administering intimin. (Chidlow at col. 2, line 59 to col. 3, line 2.) Moreover, Chidlow's comment that one may include exotoxins and other materials with endotoxins suggests that it may not be beneficial to enrich or purify any one component. (*Id.*) Craviato, in turn, adds that intimin is recognized by certain antibodies, but does not suggest that intimin in "enriched or purified" form should be administered to a host in a therapeutic protocol such as that Applicants have claimed.

In addition, the Office acknowledged that Chidlow does not teach "purified" intimin. (Office Action of August 15, 2001, at page 15.) The Office cannot remedy this defect by relying on Craviato. Indeed, the teaching of "purified intimin" that the Office cited in Craviato is not applicable to Applicants' claimed method. Instead, it is taken out of context. The Office cited Figure 6 and the related discussion of the figure for the teaching of "purified intimin." (Office Action of August 15, 2002, at page 15.) However, this figure only shows an *in vitro* assay in which the specificity of human secretory antibodies was tested. (*See* Craviato at page 1251, right column.) The object of this assay was apparently only to determine which, if any, infectious *E. coli* proteins were recognized by human antibodies taken from mothers who had been exposed to infectious *E. coli* strains. (*Id.*) In the assay, outer-membrane bacterial proteins were placed on a nitrocellulose filter. The filter was then incubated with human secretory antibodies, such that antibodies recognizing proteins on the filter would adhere to it. The protein-antibody complexes on the filter were detected by an immuno-staining procedure. (*Id.*) This *in vitro* assay is simply not relevant to Applicants' claimed

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

invention because it does not provide any suggestion that the purified intimin used in the *in vitro* assay could or should be administered to any host.

For all of these reasons, one of ordinary skill in the art applying the teachings of these publications would not have been motivated to follow Applicants' path, nor would have reasonably expected success in doing so. Thus, Applicants respectfully request the withdrawal of this rejection.

B. Rejection of claims 60, 66-71, and 73-96: Dougan in view of Chidlow

The Office rejected these claims under 35 U.S.C. § 103(a) over Dougan in view of Chidlow. Applicants respectfully traverse.

The Office contended that Dougan teaches "a conserved, receptor associated portion of intimin for administration and induction of an immune response that will block binding and treat infection," citing Dougan at col. 2, lines 43-44. However, Dougan's only mention of treatment at all is a comment made only once in passing that an antibody recognizing the carboxy-terminal amino acid region of intimin could be useful for "detection and/or treatment." (*Id.*) Dougan then focuses entirely on use of the antibodies in detection of EPEC infections. Therefore, Dougan does not teach that it would be desirable to administer intimin to any host. Moreover, its passing comment about usefulness in "detection and/or treatment" refers only to anti-intimin antibodies. Thus, Dougan as a whole provides no real motivation to use intimin or its antibodies therapeutically, and certainly no guidance as to the steps one of ordinary skill in the art could take to do so.

Chidlow does not alleviate this deficiency in Dougan, because, contrary to the Office's statement that "protection through administration of an enriched composition

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

that comprises intimin of *E. coli* 0157 antigen was carried out and claimed by Chidlow et al.," Chidlow does not refer to intimin at all, but only to endotoxins and exotoxins. (Office Action at page 6; Chidlow at col. 2, line 66 to col. 3, line 11.) As stated above, intimin is an adherence factor, not an endotoxin or exotoxin.

Because the combination of Dougan and Chidlow does not teach administering intimin to provide passive immunity, the combination of these references also does not teach or suggest that it would be desirable to administer "enriched or purified intimin." Further, as noted above, Chidlow comments that it is beneficial to administer endotoxins along with many other cellular factors or materials because many components of the infectious bacteria can have positive antigenic capabilities. (Chidlow at col. 2, line 59, to col. 3, line 2.) Thus, Chidlow suggests that it would not be desirable to "enrich or purify" any single protein factor, but to administer many factors together. In addition, the Office has acknowledged that Chidlow does not teach "purified" intimin.

Even more important, the combination of Dougan and Chidlow does not provide one of ordinary skill in the art with a reasonable expectation of success in performing Applicants' claimed methods. Neither reference suggests that "administering enriched or purified" intimin can be expected to provide patients with passive immune protection. Dougan discusses the properties of intimin in only the most minimal fashion, while Chidlow does not discuss intimin at all.

With respect to the Dean-Nystrom Abstract, Applicants reiterate that one of skill in the art would reasonably conclude from this experiment with piglets that similar results would be obtained in other species of the claimed genus. (*See* Applicants' remarks filed January 29, 2002, at pages 8-9, and citations therein.) Indeed, piglets are

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

frequently chosen as model species for immunological studies because their immune systems resemble those of humans. (*See* Amendment filed January 29, 2002, Exhibit A.) Moreover, as to the amount of titer or the source of the antibodies used, the Office has not set forth any substantial evidence showing that one of skill in the art would believe that protection could only be achieved with antibodies from a particular bodily source and of a particular titer, and with two vaccinations. (*Id.*) The Office bears the burden to present such evidence and cannot fulfill that burden with conclusory statements. *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001); *In re Lee*, , 61 U.S.P.Q.2d at 1433, 1435 (Fed. Cir. 2002) (citations omitted).

In addition, the Office stated, relying on Chidlow, that: "Evidence showing protection against infection with an enriched composition has been described in the prior art. Protection would be expected, and a showing of protection does not show unexpected results." (Office Action at page 6.) However, Chidlow, once again, does not teach the use of intimin. Therefore, these comments do not diminish Applicants' contention that the Dean-Nystrom Abstract presents unexpected results.

Because the combination of Dougan and Chidlow does not suggest the desirability of administering "enriched or purified intimin" as Applicants have claimed, and does not provide one of ordinary skill in the art with a reasonable expectation of success in doing so, Applicants respectfully request the withdrawal of this rejection.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

CONCLUSION

Applicants respectfully request the entry of new claims 97-104, the reconsideration and reexamination of the application, and the timely allowance of claims 60, 66-71, and 73-104.

If any extensions of time are needed to enter this response, please grant them. Please charge any required fees not submitted herewith to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: January 6, 2003

By: _____
Elizabeth A. Doherty
Reg. No. 50,894

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com